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REPORTING STANDARDS OF PAPERS ON THE PREVENTION AND MANAGEMENT OF FOOT ULCERS IN DIABETES:

REQUIRED DETAILS AND MARKERS OF GOOD QUALITY

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Abbreviations

ABPI	Ankle:brachial pressure index
CAD	Coronary artery disease
CONSORT	CONsolidated Standards Of Reporting Trials
EOT	End of treatment
EWMA	European Wound Management Association
FDA	US Food and Drug Administration
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
IDSA	Infectious Disease Society of America
ITT	Intention to treat
IWGDF	International Working Group on the Diabetic Foot
PAD	Peripheral artery disease
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
$TcpO_2$	Transcutaneous pressure of oxygen

REPORTING STANDARDS OF PAPERS ON THE PREVENTION AND MANAGEMENT OF FOOT ULCERS IN DIABETES: REQUIRED DETAILS AND MARKERS OF GOOD QUALITY

ABSTRACT

The evidence base for many aspects of the management of foot ulcers in people with diabetes mellitus is weak and there is a need for good quality research, especially in studies of direct relevance to routine clinical care. This paper summarises the core details required in publications of intervention studies in the prevention and management of diabetic foot ulcers, including studies of off-loading, stimulation of wound healing, peripheral artery disease and infection. It centres on those aspects of trial design, conduct and reporting which should be taken into account in order to minimise bias and increase quality. It also includes a 21-point checklist for authors and for readers who assess reports of completed work.

INTRODUCTION

Foot ulcers pose an enormous problem for people with diabetes[1], and their prevention and management are undermined by a lack of evidence upon which to base treatment choices. Repeated systematic reviews have drawn attention to the urgent need for more high quality studies in the fields of both prevention and management.[2-7] Despite this, and despite the escalating size of the clinical problem, the number of reports of high quality research on interventions for diabetic foot ulcers has remained low.[2-6]

There is no shortage of guidance available on the general principles of trial design and conduct and authors are already encouraged to use one of a number of checklists when planning and conducting their research. These include the CONSORT statement for randomised trials,[8] STROBE for epidemiological studies,[9] and PRISMA for systemic reviews and meta-analyses.[10] There also already exist systems for scoring studies of different design[11] and guidance on the evaluation of published evidence – notably the GRADE system.[12] The application of these principles for studies of chronic wounds has been embraced in two guidance documents published by the European Wound Management Association (EWMA),[13,14] but none have hitherto been produced that are specific for studies in the complex clinical area of foot ulcers in diabetes. Part of the reason for this lies in the large number of variously overlapping processes involved in the development and presentation of foot ulcers – as well as in their protracted healing – and the effect these have on all aspects of trial design.

The current paper therefore outlines standards for the conduct and reporting of studies on foot ulcers in diabetes, although it is intended to be read in conjunction with the less specific reports published by EWMA.[13,14] It is directed at those who design and undertake the research as well as at those who read and assess the report. It is hoped that by defining the criteria to be specified in research articles and by increasing the critical appraisal of

reviewers and readers, this paper will lead to an increase in the quality of the research conducted and submitted for publication. Finally, the authors have found in the conduct **A: assessment?**of repeated systematic reviews that existing tools for assessing the literature do not fully meet the needs of research in this complex clinical field, and it is for this reason that a checklist is also included as both a guide to authors and a tool for assessing the quality of reported work in this area.

This definition of standards for the design and reporting of research into disease of the foot in diabetes is limited to interventions designed to improve either the prevention or the management of foot ulcers and excludes other forms of diabetic foot disease. Although consideration is given to studies targeting different pathogenic factors such as neuropathy, deformity, peripheral artery disease (PAD) and infection, it is primarily focused on research which is of direct clinical relevance. These guidelines do not include work on specific underlying biological mechanisms or processes, observational (non-interventional) research, or work on experimental animals. The report is also limited to studies of efficacy and effectiveness and does not consider health-economic aspects.

CORE DETAILS FOR REPORTS OF INTERVENTION STUDIES

There are many details that should be documented in intervention studies but they vary depending on the specific area of research. They also vary between studies of ulcer prevention and studies of ulcer management. The details of studies can also be divided into those relating to the populations (whether of the person, the limb or the foot), interventions and outcomes, and they will vary according to the primary objective or area of interest of the study. The details of prevention studies are listed in Table 1 and those of studies on ulcer management in Table 2, with further details concerning off-loading, associated PAD and infection provided in Tables 3-5, respectively.

The items listed in the tables are those which should be considered as essential for inclusion in reports even though the detail for each will vary with study type. Failure to include some or many of these details is the reason for so few high quality papers being identified in recent systematic reviews.[2-7]

Definitions

The protocol and report should include definitions of key terms appropriate to the study, such as ‘ulcer’, ‘healing’, ‘deformity’, ‘peripheral artery disease’, ‘neuropathy’, and ‘infection’. When relevant, the definition must be accompanied by the criteria or the tests used to make the diagnosis. To facilitate uniform reporting that renders comparison of studies possible, researchers are advised to use the set of core definitions on patient characteristics, treatment and outcome which has been provided by the International Working Group on the Diabetic Foot (IWGDF).[15]

STUDIES OF FOOT ULCER PREVENTION

Population

Table 1 summarises the core data to be considered in the design and reporting of prevention studies.

The population details divide into those relating to the person and to the limb. The minimum requirements for the person details are age, gender and ethnicity, because all three are relevant to the onset of new ulcers – which are more common in men, in advancing age and in white Caucasians.[16] The presence of relevant co-morbidities such as established renal failure, immobility, and/or restricted vision should also be reported. Participants should be classified as being at low, medium, or high risk using a scheme such as that adopted by the IWGDF[17] – with classification of risk being based on the presence of neuropathy, PAD or foot deformity, previous history of foot ulceration or amputation.

Other details will depend on the focus of the study (whether, for example, it is concerned with education, footwear, or correction of risk factors such as deformity, use of footwear, or PAD). Educational studies require documentation of educational status and in studies of self-care behaviour, the capacity for self-care should be described. Documentation of social deprivation may also be relevant if it is feasible.

The volume and precision of data collection is very much affected by the size of the population being studied. The incidence of new ulceration in an unselected population with diabetes is low (approximately 2% per year in a low risk population in the United Kingdom for example) and it follows that the numbers required for any study examining the effect of an intervention on ulcer incidence in such a population would need to be very high: approximately 10,000 in order to demonstrate a reduction in ulcer indigence to 1.5% – depending on study duration, anticipated withdrawals and power. The information that can be reliably obtained from such numbers is necessarily limited, and this is in contrast to smaller studies in which more detailed data can be recorded.

Intervention

A variety of interventions may be explored with respect to prevention and these are grouped in Table 1 together with required core details. The description of the intervention should be detailed enough to enable another researcher to replicate the study. In studies of footwear, for example, it is not sufficient simply to state that the intervention was ‘custom made’: details must be provided.

As in studies of ulcer management, studies of ulcer prevention should also specify the approach taken to usual care of the foot in diabetes in the comparator group, including:

- Frequency of routine surveillance to document the degree of ulcer risk
- Approach to the mitigation of risk factors (eg deformity, abnormal pressure loading, PAD)
- Provision of foot care education
- Frequency of surveillance for those at moderately increased risk
- Frequency of surveillance for those at greatly increased risk

Outcomes

The outcomes for the foot or limb or for the person – whether they are direct or surrogate- and are listed in Table 1.

In prevention studies, the primary outcome measure is preferably the incidence of new ulceration, expressed as the proportion of the population (in both numbers and percentages) suffering a new ulcer by a fixed time and/or time to new ulceration. Ulcer definition is a

minimal requirement. If more than one ulcer risk group is included, outcomes should be reported for each group separately. In some instances it will also be important to record the ulcer type and site, and when it is a recurrence (i.e. a foot ulcer at the same site on the same foot as the previous ulcer) or an ulcer at a new site.

Because very large numbers may be required to study prevention in lower risk populations, it is usual to base research on populations at high risk. The highest risk group includes those that have had an earlier ulcer. The incidence of ulcer recurrence is of the order of 30-40% in the first 12 months after healing.[18-19] Other prevention studies may use surrogate measures such as change in foot self care (for educational/behavioural or other psychological intervention studies directed at patients), change in foot examination skill or frequency (for professionals), and change in foot pressure (for footwear).

Any study on the effect of footwear or surgery on plantar foot ulcer incidence should provide evidence of the efficacy of these interventions to reduce pressure underneath the foot, based on barefoot or in-shoe measures made with a validated plantar pressure measurement system. Additionally, footwear studies should provide data on adherence to wearing the prescribed shoe using diaries or, preferably, wearable technology such as activity and footwear use monitors For self-care management, data on adherence and false-positive and negative outcomes in seeking professional help are important as they can contribute to the cost-effectiveness and acceptance of the intervention in clinical practice.

STUDIES OF THE MANAGEMENT OF EXISTING DIABETIC FOOT ULCERS

Core details for inclusion in reports of clinical studies assessing treatments of established foot ulcers in diabetes are listed in Table 2. Further details for studies on off-loading, PAD and infection are listed in Tables 3-5, respectively. The following additional points should be considered.

Population

When the population studied is a mixed one (for example, studies including both venous ulcers of the lower leg and diabetic foot ulcer or studies including both people with and without diabetes), it is essential that the sub-population of interest – those with diabetic foot ulcers – is separately described and analysed, with specific reference to sample size, baseline characteristics, withdrawals and outcome. History of previous ulceration or amputation may also be important and should be specified in studies that include recurrence or new ulceration as an endpoint. The setting in which the study was conducted (primary/secondary/ tertiary care; single- or multicentre) should be described in order to indicate its generalisability.

Person and limb

The extent of co-existing neuropathy, PAD and deformity should be documented since all can contribute to ulcer onset The minimum requirement for defining neuropathy (ie loss of protective sensation) is usually accepted as foot sensation documented with a 10g monofilament, although some researchers may use a different stimulus (such as vibration perception) The minimum details currently accepted for defining the presence of PAD in any ulcer study are pulse palpability and the ankle-brachial pressure index (ABPI). Neither of these measures are without flaws, however, and further tests may be required depending on the nature of the study (see Table 4). In studies involving vascular interventions on both legs, one limb should be chosen as index leg and only the findings of this leg should be reported. There is no accepted way of documenting the degree of foot deformity in clinical

practice. Its inclusion is, therefore, inevitably subjective. But if foot deformity is relevant, then an attempt should be made to describe its nature and severity.

Ulcer

The ulcer needs to be described. There are a number of classification schemes available to document ulcer characteristics.[20] Not all of these schemes include all the details required for all studies. Reports should, however, specify the details listed in Table 2.

Multiple ulcers
People often have more than one ulcer and the overall prognosis is worse in those that do. In individuals with multiple ulcers, one ulcer should usually be selected for the study (and is termed the 'index ulcer'. The index ulcer is usually the largest or the one judged clinically to be the most important, even though this depends on the chosen study criteria. In studies in which the endpoint selected is healing of all ulcers (and the foot being ulcer-free), then all are considered together as a group.

Area, depth and site
Both greater area and greater depth are associated with healing delay and both need to be documented, as do the methods used to determine them. Area is usually documented after debridement but this needs to be stated. Ulcer depth is best classified by anatomical depth (as in the University of Texas, IWGDF and SINBAD classification systems[20]) and not in mm. Anatomical site should be specified because of the impact of site on choice of intervention and on the rate of healing.

Infection
The diagnosis of infection is primarily clinical and is based in the criteria of the Infectious Diseases Society of America (IDSA) and the IWGDF.[21] Studies may or may not include ulcers which are infected at recruitment but if they do, the definition and severity of infection needs to be described. For studies where infection is the primary interest, see Table 5.

Selection of the 'hard-to-heal' ulcer

In assessing the effectiveness of new treatments for wound care and off-loading, it is becoming more common to specify that the study ulcer has failed to heal despite management in a specialist centre according to accepted principles of good standard care (see below). This requires that the duration of the ulcer is defined and that it has persisted without reducing by more than a stated percentage in cross-sectional area (40 or 50%), or other aspect of size (eg diameter, depth, volume). The logic for this is that new (and often expensive) treatments should usually not be used for ulcers that are likely to heal with good standard care. The adopted principles of good standard care must be described (see below).

Nevertheless, the 'hard-to-heal' group may include ulcers that have sometimes been present for very long periods and their failure to heal may derive from a complex interaction of biological, social and personal factors. In such cases, the chances of a single treatment being shown to be effective may be reduced. This possibility might be reduced by including an upper limit for ulcer duration (such as 12 or 24 months).

Intervention

The management of diabetic foot ulcers is multifaceted and the intervention to be tested will usually be provided *in addition* to general good standard care.

‘Good standard care’ and ‘usual care’

The design of many studies will involve comparing outcome in those receiving the intervention *plus* good standard care with the outcome in a similar group receiving a different intervention *plus* good standard care or a group receiving good standard care alone. On occasion the comparator group may be managed with ‘usual care’ – implying no effort has been made to ensure that such care fulfils all the criteria of good standard care. While this is not ideal, it may be a pragmatic solution – particularly in a study designed to document effectiveness in a large population as opposed to efficacy in smaller, more tightly defined, one

Good standard care

The principles of good standard care are grouped as follows:

- Formal assessment of the ulcer and surrounding skin at each clinic review
- Provision of any necessary off-loading, with detailed description of the type and assessment of its effectiveness
- Debridement of the wound surface which may be surgical/’sharp’ (either in the clinic/office or in an operating room) or non-surgical
- Selection of appropriate dressing products
- Appropriate antibiotic therapy (for clinically infected wounds only)
- Attention paid to nutrition and self-care
- Attempt to achieve optimal glycaemic control
- Assessment for peripheral artery disease, with consideration of revascularisation where appropriate
- Continued close observation with appropriate adjustment of management

Outcome

Outcomes can be person-related, limb-related or ulcer-related and core details are listed in Table 2.

Person and limb-related outcomes

The outcome that most people want is to survive, have improved quality of life, optimal mobility and to be ulcer-free as soon as possible, without the need for surgery or hospital admission – and without recurrence. Overall long-term outcome of the intervention may therefore be survival (at a fixed time) without continuing ulceration and with unaided mobility intact. The use of quality of life measures should also be considered.

Surgery

If a person undergoes surgery, its nature needs to be defined:
- surgical debridement with/without local intervention such as grafting
- minor amputation (which is defined as transverse removal of part of the lower limb below the ankle joint)[15]
- major amputation (transtibial, through knee, transfemoral)[15]

Consideration should be given to documenting the extent of any post-operative morbidity (eg wound infection, transfer ulceration). When surgical or endovascular procedures are evaluated, 30-day mortality should be reported, and preferably also long-term mortality.

Amputation and Mortality

The incidence of major amputation should never be considered in isolation from death. The reason for this is that there are many people who die during follow-up and who would have had a major amputation if their overall prognosis was not so poor. It is also acknowledged that early major amputation may be the best treatment for a number of people. It follows that while the incidence of limb loss through amputation should be recorded, it is also necessary to document death during the study – both with and without preceding major amputation.

Limb salvage

The term 'limb salvage' (meaning survival without major amputation) has become popular in some specialty areas, but it is poorly defined and is not therefore recommended. The term 'amputation-free survival' is to be preferred.

Ulcer-related outcomes

Ulcer healing and time to healing

Ulcer healing is usually defined as complete epithelialisation after removal of callus without discharge, which is maintained for a minimum of two weeks (as currently required by the FDA) or longer. Any ulcer that occurs after the time specified in the definition of healing, is regarded as a recurrence. It is important also to specify whether healing follows a surgical procedure (such as flap or grafting) or whether it is by secondary intention. Healing can be recorded as the number (or percent) of index ulcers healed by a fixed time from randomisation (or the start of the observation period in non-randomised studies), or it may be recorded as time to healing. The term 'rate of healing' is ambiguous because it may refer to the incidence of healing, to the time to healing or to the percentage reduction in cross-sectional area and should therefore be avoided.

A further problem inherent in the use of either the number (percent) of ulcers healed by a fixed time or the time to healing is that it is directly related to baseline ulcer area – because larger ulcers take longer to heal. It is, therefore, important to ensure that intervention and control groups include near equal numbers of ulcers of different area.

Change in ulcer area

Change in ulcer area may be used as a surrogate endpoint, but measurement of ulcer area presents its own problems. The contour of the foot underlying an ulcer is nearly always curved and this means that measurements taken from digital images are not precise. It is, therefore, important that the methods used to measure cross-sectional area are documented. Newer commercial imaging systems are also available and are increasingly used but they tend to be expensive. Some such systems may, however, allow the option for assessment of changes in ulcer volume.

Infection

Outcomes relating to infection are listed in Table 5.

The aim of most studies will be resolution of infection. This is defined as the disappearance of, or sufficient improvement in, signs and symptoms related to the infection such that it does not require further treatment. Resolution of infection may be achieved either by the use of non-surgical antimicrobial treatment (including antiseptics or antibiotics, by topical, local or systemic routes) or by antimicrobial therapy in combination with surgery. If the study is concerned with the evaluation of an antimicrobial regimen, then the use of surgery may be

considered as an outcome (indicating incomplete effect) whereas in studies of a combined approach, it may simply be a detail of the intervention.

In the evaluation of non-surgical interventions (such as an antibiotic regimen), the resolution of infection can be determined at different stages – including during specified points during treatment, at the End of Treatment (EOT) or at a specified time after EOT, usually called Test of Cure. Such studies often also include microbiological outcomes but consideration of these is beyond the scope of this article.

Ulcer healing is not a specific measure of the resolution of infection. The eradication of clinical infection can also not currently be defined by the results of microbiological testing.

Other outcome measures

A number of other ulcer-related outcomes may be selected – especially in shorter-term studies that involve the use of surrogate endpoints, including measures of clinical wound appearance and status.

Adverse events

Any study of an intervention must include formal documentation of adverse events and adverse device effects (whether or not they are serious). Adverse events may include, but are not restricted to, new ulcers at another location, hospitalisation, abrasions, other pre-ulcerative lesions, infection, induction of an acute Charcot foot and falls.

Adherence

It is not possible to assess the efficacy or effectiveness of an intervention unless the completeness of intervention delivery has been documented. One example relates to the use of off-loading in which it can be important to demonstrate not only that off-loading has been prescribed, but that it is effective in terms of reducing the forces applied to the foot or to the healing wound and that the device is worn (compliance/adherence/concordance).

MANAGEMENT STUDIES INVOLVING TREATMENTS DIRECTED SPECIFICALLY AT PERIPHERAL ARTERY DISEASE IN PEOPLE WITH DIABETIC FOOT ULCERS

Populations in studies in which the primary focus of interest is on interventions for PAD need to be defined using more precise anatomical and functional markers of PAD. Similarly, the interventions and the outcomes will be specific to revascularisation, even though ulcer healing may be used as a secondary outcome measure. Core details are listed in Table 4. It should be noted that none of the existing classifications for the effects of PAD is entirely appropriate for people with diabetic foot ulcers,

MANAGEMENT STUDIES SPECIFICALLY DIRECTED AT THE PREVENTION OR TREATMENT OF INFECTION IN PEOPLE WITH DIABETIC FOOT ULCERS

The additional details required in studies particularly directed at the management of infection are listed in Table 5.

Careful definition will be required for both the population and the outcome. In the majority of cases, however, studies will be concerned with the treatment of clinically overt foot infection,

as defined and classified by the IWGDF and the Infectious Diseases Society of America (IDSA).[23,24] Such studies may select those with either soft tissue infection alone or soft tissue infection combined with osteomyelitis. The criteria used to define or exclude any osteomyelitis must be stated.

MARKERS OF GOOD QUALITY: STUDY DESIGN, CONDUCT AND REPORTING

Some of the details in the above sections should be used to define the quality of the resulting publication. These are listed in Table 6, although some notes regarding interpretation and use are added below.

Quality

The term 'quality' largely refers to the extent to which a study and its report are free from bias. In this respect, the term 'freedom from bias' indicates that the reported observations and conclusions are most probably the result of the intervention and relatively unlikely to have been affected by other influences. Many of the criteria listed overlap with the CONSORT list[8] which is widely applied by journal editors when considering papers for publication and many are also discussed with relevance to the management to studies of chronic wounds in two publications by EWMA.[13,14] This particular checklist is designed for intervention studies in the field of diabetic foot ulcers.

Grading and scoring

In addition to providing guidance to the researcher on the design and reporting of research in this field, the aim of this checklist is to include criteria that can be used to grade the quality of the report and thereby give an indication of its potential relevance to routine clinical practice. The ability to grade publications in this way is of great importance – partly in the assessment of individual publications and partly for the conduct of systematic reviews. A number of generic scoring schemes already exist but the experience of the authors is that these do not apply well to this particular clinical problem.

The selected points are divided into four main groups: study design, study conduct, outcomes and study reporting. The intention is that the desired answer for each item is "Yes", and that each scores one point. Criteria have yet to be established to determine how the resultant scores (maximum 21) can be stratified into appropriate levels of quality.

Item 2 Appropriate population

If the study is being assessed from the point of view of clinical care, the following principles apply – even though there will be some exceptions.

- The participants should be humans with diabetes and who are either at risk of (for prevention studies) or complicated by (for treatment studies) a diabetic foot ulcer
- If more than one foot ulcer is present, it should be properly described, and usually only one ulcer (a specified 'index' ulcer) should be included per participant if a change in ulcer status is to be used as an outcome measure (see below).
- The type of ulcer chosen for study should be appropriate for the type of intervention being tested. This is relevant because many older trials of new interventions were conducted on people with uncomplicated neuropathic ulcers – for which a cheap and effective treatment already existed (i.e. off-loading). In practice, a new (and usually expensive) treatment will be reserved for those ulcers which have already failed to heal despite administration of good standard care in expert centres. It follows that the effectiveness of new treatments should usually be assessed in participants with such 'hard-to-heal' ulcers. To that end, the term, 'hard-to-heal', requires definition.

Item 4 Description of intervention

The description should be detailed enough to enable another researcher to replicate the study. For example, in studies of footwear it is not sufficient to state that the intervention was "custom-made"; details of the customisation must be described.

Item 5 Definition of other aspects of care

When an intervention is administered for either the prevention or the treatment of diabetic foot ulcers, it will inevitably be administered in conjunction with other aspects of care (whether 'usual' or optimised as good standard care, see above). The components of other aspects of care must be described.

Item 9 Relevance of the primary outcome

This article is concerned primarily with studies which might have an impact on clinical care. The emphasis is therefore on outcome measures of direct clinical relevance.

Item 13 Retention/attrition

Many participants are lost to follow-up from studies in this field – not least because the population susceptible to foot disease is also susceptible to other complications of diabetes and co-morbidities and it is not uncommon for them to suffer intercurrent illness. The longer the study lasts, the more likely this is to happen and if the primary outcome is based on ulcer healing, then it is likely that the duration of the intervention may be for as long as 16, 20 or 24 weeks. If the primary endpoint is ulcer development in a prevention study, follow-up may be much longer. The lower the rate of retention (i.e. the higher the rate of attrition), the greater is the likelihood of bias in any observation made.

There is no consensus on the rate of retention/attrition which is acceptable in this population in studies of differing duration but in the opinion of the authors, the rate of attrition should be no greater than 25% in studies of ulcer management with an intervention phase of 20 weeks or more.

Item16. Performance in the control group

Some expensive new interventions have acquired widespread adoption as a result of studies that would now be regarded as flawed. In some cases this was because the apparent benefit of the new intervention was based on demonstrating a significant difference from the comparator group when the difference could be accounted for by poor performance in the usual care group. It is, therefore, essential to scrutinise performance in the comparator group and, in addition, to check that it is similar to that which was used as the basis for any sample size calculation.

SUMMARY AND CONCLUSIONS

The article is based on expert opinion and summarises the points that should be included in the design and reporting of clinical studies of the complex processes involved in the prevention and management of ulcers of the foot in diabetes. It is directed both at researchers planning clinical research in this area and at those that read and assess the reports of such work. It does not include detail on some more fundamental aspects of trial design which are covered in previous publications by EWMA.[13][14] Finally, it is intended also to be used as a template and one which will need further detail for studies in some subspecialty areas.

The production of lists of required data is fraught with difficulty, not least because the details required for one sort of study may sometimes be quite different from those required in another, even in the same field. It is this difficulty which results in Tables 1-5 being entitled 'Core details because it is not possible to be more dogmatic. This is most true in the specific subspecialty areas of offloading, PAD and infection. For each of these, as well as for research relating to specific interventions in the field of wound healing, the lists provided will ultimately serve as no more than a spine that can be used for the more detailed guidance required by those working in the area.

In addition to highlighting the core details for points to be considered in trial design and for inclusion in published reports, this paper incorporates a checklist of 21 items which can be used to assess the quality of work in this area. The higher the score achieved, the greater the chance that the reported study is free from bias and is relevant to clinical practice. This checklist aims to provide equal weight to aspects of study design, conduct and reporting and should be considered as a tool for the performance of systematic reviews in this complex clinical area.

CONFLICTS OF INTEREST

All of the authors (WJJ, SAB, FLG, RJH, PEP, NCS) declare no competing interests.

AUTHOR CONTRIBUTION STATEMENT

All authors were involved in discussions leading to the drafting of this manuscript. WJJ, SAB, FLG, PEP and NCS produced the first version of the manuscript in its final form, while WJJ, SAB, FLG, RJH, PEP and NCS were all involved in the responses to the editor and the reviewers and agreed the revision of the manuscript

CONFIRMATION OF ORIGINALITY

This paper has not been submitted to another journal and has not previously been published in whole or in part elsewhere.

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TABLE 1

CORE DETAILS FOR THE REPORTING OF INTERVENTION STUDIES
(A) PREVENTION OF FOOT ULCERS IN DIABETES

Population

Person

- Age, gender, ethnicity
- Co-morbidities (e.g. renal failure, heart failure, impaired vision)
- Ulcer risk classification: low, medium or high
- Ambulatory status
- Educational status, socio-economic status capacity for self-care (for studies on education)

Limb

- PAD: minimal assessment by palpation of pulses and ABPI and/or toe BP
- Neuropathy: minimal assessment by determining loss of protective sensation (eg 10g monofilament or vibration perception)
- Foot deformity (type and/or severity)

Intervention

All interventions

- Details of interventions, including duration/frequency
- Person or team providing foot care and the setting of the study

Footwear specific interventions

- Details on design, customisation, materials used
- Evidence of pressure-reducing efficacy if study relates to plantar ulceration

Education/behavioural change specific interventions

- Whether aimed at the patient or professional

Surgical interventions

- Evidence of pressure-reducing efficacy if study relates to plantar ulceration.

Outcomes

Foot/limb

- Ulcer (defined according to existing guidelines) incidence expressed as a proportion of a population in a fixed time, and/or time to ulceration
- First ever ulcer
- Recurrent ulcer, specified to either being at the same site or at a different site
- Adherence to the intervention (eg wearing footwear, to self-care or to education, preferably measured objectively)
- Foot pressure reduction (following provision of footwear and/or surgical interventions)
- Ambulatory activity level (for footwear studies), expressed as quantitatively as possible
- False-positive and negative outcomes (in diagnostic self-care studies)
- Amputation (with exact level defined according to existing guidelines)

Person

- Survival
- Ulcer free survival (days)
- Health-related quality of life
- Adverse events

Surrogate

Potential surrogate outcome measures for studies in which ulcer incidence is not the primary outcome

- Incidence of pre-ulcerative lesions (eg hyperkeratotic tissue, haemorrhage, blister, inflammation – each of which require definition)
- (Change in) plantar foot pressures
- (Change in) adherence
- Knowledge (patient, carer, professional)
- Behaviour (patient, carer, professional)
- Foot examination skill (patient, carer, professional)
- Patient satisfaction, and well-being

TABLE 2

CORE DETAILS FOR THE REPORTING OF INTERVENTION STUDIES
(B) MANAGEMENT OF EXISTING DIABETIC FOOT ULCERS

See also relevant details in Tables 3, 4 and 5

Population

Person

- Age, gender, ethnicity
- Diabetes type, duration and adequacy of glycaemic control
- Co-morbidities (renal failure, heart failure, impaired vision)

Limb

- PAD: minimal assessment by palpation of pulses and ABPI
- Neuropathy: minimal assessment by loss of protective sensation (eg 10g monofilament or vibration perception)
- Foot deformity (individual deformities or severity of deformity)
- History of previous foot ulceration and amputation

Ulcer

- Number of active ulcers
- Site of index ulcer
- Duration of index ulcer
- Type or classification of index ulcer (where appropriate)
- Area, depth
- Presence or absence of infection

Intervention(s)

There are multiple potential interventions and these may be administered systemically, regionally or topically. For each intervention sufficient information must be provided to define

- its nature (including source)
- route, frequency and duration of delivery
- delivery by whom: professional, non-professional carer, self
- place of delivery: domiciliary, community clinic or surgery, hospital, specialist centre

Details of interventions relating to off-loading, treatment of PAD and infection are outlined separately in Tables 3, 4 and 5.

Outcome(s)

Person

- Survival
- Being ulcer-free and/or amputation free at a fixed time after presentation
- Ulcer-free survival days
- Adverse events and/or adverse device effects
- Health-related quality of life

Ulcer and limb

Direct

- Ulcer healing (defined, according to existing guidelines eg IWGDF); time to healing
- Healing following local surgery, including operative debridement
- Failure to heal by a fixed time – ulcer persistent
- Amputation (with exact level defined according to existing guidelines)

Surrogate

- Change in ulcer area by a given period of time
- Change in ulcer appearance, biochemistry, histology or other laboratory measure of wound bed status

TABLE 3

CORE DETAILS FOR THE REPORTING OF INTERVENTION STUDIES
(C) STUDIES OF OFF-LOADING IN THE MANAGEMENT OF EXISTING DIABETIC FOOT ULCERS

Population

See Table 2

Intervention

Non-surgical

- Details on device, application method, material use, frequency of replacement
- Specific design details of the foot-device interface
- Professional / person applying the device
- Evidence of pressure-reducing efficacy if study is on plantar ulceration

Surgical

- Details of intervention
- Evidence of pressure-reducing efficacy if study is on plantar ulceration

Outcomes

Person
See Table 2.

Ulcer/limb

- Ulcer healing (see general items for this under ulcer healing)
- Complication rate/adverse events, whether serious or not (i.e. infection, hospitalisation, amputation, mortality, intervention-induced ulcers, abrasions, blisters, hyperkeratotic tissue, inflammation)
- Adherence to the use of non-surgical removable interventions
- Foot pressure (for footwear and surgical interventions)
- Ambulatory activity level

TABLE 4

CORE DETAILS FOR THE REPORTING OF INTERVENTION STUDIES FOR EXISTING DIABETIC FOOT ULCERS
(D) STUDIES INVOLVING INTERVENTIONS DIRECTED SPECIFICALLY AT THE MANAGEMENT OF PERIPHERAL ARTERIAL DISEASE

These details are in addition to those listed in Table 2.

Population

Person

- Smoking status
- Ambulatory status
- Previous PAD interventions
- History of PAD-related disease: CAD, heart failure, cerebrovascular disease
- Other relevant comorbidities (eg renal disease, depression)
- Relevant cardiovascular medication

Limb

- Symptoms: none, atypical (weakness, limping), intermittent claudication, rest pain
- Toe systolic pressure, toe-brachial pressure index and/or transcutaneous partial pressure of oxygen ($tcpO_2$)
- Arterial pulse waveform
- Anatomical distribution of the vascular disease in the leg.

Ulcer

- Number of active ulcers
- Site of index ulcer

Outcomes

Person
See Table 2

Limb

- Number of subjects alive with an intact foot
- Ulcer healing
- Description of outflow in the foot (in case of surgical or endovascular interventions)
- Measures of the effectiveness of the vascular intervention (e,g. toe pressures, $tcpO_2$)
- Number of patients with minor and with major amputations

TABLE 5

CORE DETAILS FOR THE REPORTING OF INTERVENTION STUDIES
(E) STUDIES THE MANAGEMENT OF INFECTION IN EXISTING DIABETIC FOOT ULCERS

Population

In addition to the detail in Table 2 information is required on the following.

Person

- Preceding antibiotic use (type, route, duration, time before presentation)
- Immunosuppression

Infection

- Infection type (using IDSA/PEDIS grading): none, mild, moderate, severe
- Involvement of bone or joint
- Description how samples were obtained for microbiological examination
- Type of and results of microbiological examination (Gram stain/susceptibility)

Intervention

- Surgery undertaken prior to or in association with antibiotic (or non-antibiotic antimicrobial) administration
- Any other relevant intervention (including wound debridement, cleansing and antiseptic use) undertaken prior to or in association with antibiotic (or non-antibiotic antimicrobial) administration
- Antibiotic (or non-antibiotic antimicrobial) regimen(s) (route, agents, duration)

Outcome

The choice of outcome will be determined by the study design and, in particular, whether the aim is to assess the use of a non-surgical antimicrobial treatment without surgery or to evaluate an intervention which combines the two. In addition to those listed in Table 2 (but excluding ulcer healing) these include

- Resolution of infection (which should be defined), at a pre-specified time after stopping antibiotic treatment
- Clinical and/or laboratory signs of persistent infection at end of antibiotic treatment
- Number and type of surgical procedures, including amputation (with level of amputation defined according to existing guidelines)
- Days of antibiotic use; antibiotic-free days; days of hospital admission
- Prevalence of antibiotic resistance following treatment

Person outcomes

- See Table 2.

Table 6

21-point scoring system for reports of clinical studies of the prevention and management of disease of the foot in diabetes.

Study design – population

1. Are appropriate definitions included for the terms ‘ulcer’, ‘healing’ and all other required aspects of the population and the outcomes?
2. Is the choice of study population appropriate for the choice of intervention and for the stated conclusions?
3. Was there a control population which was managed at the same time as those in the intervention group(s)?

Study design - intervention

4. Is the intervention sufficiently well described?
5. Were the components of other aspects of care described for the intervention and comparator groups?

Study design and sample size

6. Were the participants randomised to intervention and comparator groups?
7. Were the participants randomised by an independent person or agency?
8. Was the number studied in the trial based on an appropriate sample size calculation?

Study design – outcome measures

9. Was the chosen primary outcome of direct clinical relevance?

Study design – blinding

10. Was the person who assessed the primary outcome(s) blinded to group allocation?
11. Were either the clinical researcher who cared for the wound at research visits or the participant (patient) also blinded to group allocation?

Study conduct – recruitment

12. Did the study complete recruitment?

Study conduct – retention/attrition/protocol violation

13. Was it possible to document the primary outcome in 75% or more of those recruited?

Study conduct – analysis

14. Were the results analysed primarily by intention to treat (ITT) analysis?
15. Were appropriate statistical methods used throughout?

Observations – realistic performance of comparator group

16. Was the performance in the control group of the order that would be expected in routine clinical practice?

Observations – equivalent results from all participating centres

17. Were the results from all participating centres comparable? Answer ‘Yes’ if the study was single-centre.

Study reporting – missing or inconsistent data

18. Is the report free from errors of reporting such as discrepancies between data reported in different parts of the paper?

Study reporting – strength and weaknesses of the study

19. Are the important strengths and weaknesses of the study discussed in a balanced way?
20. Are the conclusions supported by the findings?

Study reporting – declaration of potential conflicts on interest

21. Is the report free from any suggestion that the analysis or the conclusions could have been significantly influenced by people with a commercial or other personal interest in the findings?